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The purpose of these investigations is to determine whether symptoms of acute mountain sickness (AMS) are affected by menstrual cycle phase and oral contraceptives in women and whether the severity of AMS differs from men. The experiments consist of 12-hour exposures to a simulated altitude of 16,000 ft. Measurements of global and regional (brain magnetic resonance imaging) fluid homeostasis, ventilation, cognitive and autonomic function are emphasized in relation to control measurements and AMS symptoms. Nineteen women have been tested in both luteal and follicular phases of the menstrual cycle, confirmed by blood progesterone levels, and 13 on oral contraceptives. There is no difference in the severity of AMS symptoms during the luteal and follicular phases of the menstrual cycle, but women increase their ventilation at altitude more when in the luteal phase. The data collected to date does not suggest that taking oral contraceptives will serve to reduce AMS symptoms. Also, no significant difference in AMS susceptibility between men and women has been demonstrated. Preliminary results also suggest that total body water changes are directly related to AMS in all subjects. AMS in these acute exposures is not related to pulmonary gas exchange deterioration or to altitude-induced changes in the transcapillary albumin exchange rate or plasma volume.

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Jack Loeppky 26 Oct 98

PI - Signature Date

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INTRODUCTION

This is the second annual report of the study entitled "The Physiology of Acute Mountain Sickness in Women." It summarizes the established methods, which were described in detail in the first report of last year, and those results available to date. An abstract, essentially as submitted with the initial contract application in November of 1995, describes the overall objectives:

"Women are becoming more prevalent as military personnel, but we lack basic knowledge about their physical and mental performance at high altitude. Military personnel deployed to high altitudes will be exposed to the hazards of hypobaric hypoxia and a significant number are at risk to develop acute mountain sickness (AMS). The deleterious impact of AMS on military operations has been demonstrated in both experimental studies and actual conflict. However, very few laboratory or field studies have examined AMS in women. Also, no laboratory studies have compared the responses of women and men exposed to high altitude. Thus, as more women are included in a wider variety of Army units, AMS can potentially result in a significant loss of unit strength and could jeopardize the accomplishment of a unit's mission. We are planning to study the effects of the menstrual cycle and oral contraceptive use in women on AMS and compare the results with men. The measurements for comparison will focus on fluid balance and distribution, including brain scans for cerebral edema, ventilatory and circulatory responses, autonomic nervous system function and cognitive function. In the past two years, in related studies, we have collected important data that began to address each specific aim and established that we are capable of the careful execution and analyses of the proposed study. This study will make a major contribution to the understanding of the requirements of female soldiers and other military personnel who may be exposed to high altitude."

To date (October 15/98) the data collection completed is about 83% of the total proposed, compared to 12% at the end of the first year. The data collection for the males and the menstrual cycle portion of our study has been completed. We anticipate that data collection for the oral contraceptive portion of the study will be completed by the end of December 1998.

BODY

A. Experimental Methods and Procedures:

In order to give an overview of the experimental logistics, test procedures and methods that are being used, we have summarized below the pertinent experimental procedures and measurements.

Appendix 1 is a detailed chronological list of the measurements as they are taken, similar to that given in the last report.

Abbreviations:

ECW: extracellular water

PV: plasma volume

TBW: total body water

D_2O: deuterium oxide

GFR: glomerular filtration rate

TCER: transcapillary escape rate

LL: Lake Louise AMS symptom questionnaire

ESQ: environmental symptoms questionnaire

VA: visual analog test of symptoms

elect: Na+, K+

6 hormones: epinephrine, norepinephrine, aldosterone, atrial natriuretic peptide (ANP), antidiuretic hormone (ADH) and plasma renin activity(PRA)

PD: plasma density

PP: total plasma protein

CPT: cold pressor test

HVR: hypoxic ventilatory response test (poikilocapnic and isocapnic)

HCVR: hypercapnic ventilatory response test

General

These measurements times shown below assume that the exposure on the chamber day to 426 mm Hg (=16,000 ft or 4,877m, according to West (1)) is for exactly 12 hours. In the event that the decision is made to curtail a run, because of intolerable AMS or for other

reasons, the measurements or procedures scheduled for the last measurement period are started early. This schedule assumes that 3 hrs are required for the ECW-NaBr test (one sample after 3 hrs) and 3 hrs are required for TBW-D_2O (one sample after 3 hrs) and that 30 min minimum are needed for the PV-Evans blue test (3 samples at 10 min intervals) and that TCER-Evans can be obtained from a 3 hr slope of Evans (3 early samples and additional samples after 1, 2 and 3 hrs). Also, Water intake equals urine output at time zero and intake is matched to output of the previous 3-hr interval. GFR will be estimated from creatinine clearance. Respiratory measurements are made with an automated system (Consentius Technologies, East Sandy, Utah) with incorporated software. Measurements include total ventilation (V_E), oxygen uptake (VO_2), carbon dioxide production (VCO_2) and R and other calculated variables. End-tidal O_2 and CO_2 are measured separately from the breathing valve (Hans Rudolph, model 2600) with an MGA-1100 mass spectrometer. Arterial samples are obtained from a single femoral artery stick during the respiratory measurements on the control day and during the first and last hour at altitude. Arterial samples include $PaCO_2$, PaO_2, SaO_2, pH and SaO_2, all measured on a Radiometer (model 520) blood gas analyzer. Hemoglobin (Hb) is measured separately on an OSM-3 Hemoximeter (Radiometer, Copenhagen).

TIME OF MEASUREMENTS

Day 1: Control day, Day 2: Altitude day

Weight: Day 1: 7:00 PM

Day 2: 7:00 AM, 10:00, 1:00 PM, 4:00 PM, 7:00 PM

Body Temp: Day 1: 7:00 PM

Day 2: 7:00 AM, 1:30 PM, 7:00 PM

HVR and HCVR: on control day afternoon

3-breath tests: on control day afternoon and after 1, 6, and 12 hr in chamber

Maximal Exercise: before control day

Cold pressor test: on control day afternoon

Respiratory (ventilation)

Day 1:	Day 2:
6:30 PM + arterial blood	8:30 AM (1) + arterial blood
	1:30PM (6)
	6:30 PM (12) + arterial blood

Symptoms (LL+VA's)

Day 1:	Day 2:
2:30 PM (practice)	6:30 AM (0)
6:00 PM add ESQ	8:00 AM (1) add ESQ
	1:00 PM (6) add ESQ
	6:00 PM (12) add ESQ
	8:30 PM, Post MRI

Heart rate & blood pressure

Day 1:	Day 2:
6:30 PM	8:30 AM (1)
	1:30 PM (6)
	6:30 PM (12)

Cognitive testing

Day 1:	Day 2:
2:00 PM (practice)	8:30 AM (1)
6:30 PM	1:30 PM (6)
	6:30 PM (12)

Spirometry

Day 1:	Day 2:
6:30 PM	8:30 AM (1)
	1:30 PM (6)
	6:30 PM (12)

Fluids:

1) TBW (D_2O) Day 1: Drink 4:00 PM - sample 6:00 and 7:00 PM
Day 2: Drink 4:00 PM - sample 6:00 and 7:00 PM

(2) ECW (NaBr) Day 1: Drink 4:00 PM - sample 6:00 and 7:00 PM
Day 2: Drink 4:00 PM - sample 6:00 and 7:00 PM

(3) Plasma Volume (Evans) Day 1: Inject 4:00 PM- sample 4:10 PM, 4:20 PM, 4:30 PM
Day 2: Inject 4:00 PM- sample 4:10 PM, 4:20 PM, 4:30 PM

(4) TCER (Evans) Day 1: Inject 4:00 PM- sample as above plus 5:00, 6:00 PM, 7:00 PM
Day 2: Inject 4:00 PM- sample as above plus 5:00, 6:00 PM, 7:00 PM

(5) Urine (volume):

Day 1:	Day 2:
6:00 AM void and balance	5:00 AM void and balance

4:00 PM void and drink	7:00 AM void and drink
7:00 PM (collect)	10:00 AM (collect, 0-3) and drink
	1:00 PM (collect, 3-6) and drink
	4:00 PM (collect, 6-9) and drink
	7:00 PM (collect, 9-12) and ad lib

Albuminuria, urine elect, osmol and creatinine for GFR

Day 1:	Day 2:
7:00 PM	10:00 AM (1)
	1:00 PM (6)
	4:00 PM (9)
	7:00 PM (12)

Venous blood: creat (for GFR), elect, PP, osmol, PD, Hct, 6 hormones, extra plasma

Day 1:	Day 2:
6:00 PM	8:30 AM (1)
	1:00 PM (6)
	6:00 PM (12)

Venous blood: progesterone Day 1: 7:00 AM Day 2: 6:00 AM

Venous blood: Epi, Norepi Day 1: taken before and during last min of CPT.

Determination of menstrual cycles

The projection of menstrual cycle dates for scheduling experiments were accomplished by a combination of interviews, previous dates of menses and daily recording of oral temperature (taken in the morning). When the calendar dates were established the subject was tentatively scheduled one or more months in advance and the projected date of the LH surge was confirmed with an LH kit by the subject during the previous or current cycle. The date of elevated progesterone in the luteal phase was usually confirmed in the cycle before the one in which experiments were done by blood progesterone assays. The control day (preceding the chamber day) for the luteal cycle was scheduled on about the 4th day following the LH surge, depending on subject's cycle length and blood progesterone levels measured periodically in weeks preceding actual experiments. A blood progesterone level of 6 or more ng/ml defined the luteal phase. The progesterone values shown in table 1B and 1C for the

women subjects are the average of values measured on the control and altitude days to confirm cycle phase. Blood progesterone was measured using a microparticle enzyme immunoassay (MEIA) technique (Abbott).

Experimental schedule of women on oral contraceptives (OCP)

Women taking OCP's are being studied once near the end of the week when on the placebo pill (C) and once near the end of the week when they receive the highest progestin level pill (usually the third week of the pill cycle). We plan to study half of the women first during the placebo week and half first during the high progestin week.

The basic assumption for this study is that as subjects develop AMS symptoms, the progressive severity over the 12 hours in hypoxia will correlate with many of the variables measured during the course of the altitude exposure, thus helping to explain the pathophysiology. The exercise, autonomic and ventilatory measurements taken on the control day will also be tested regarding their validity in predicting AMS for particular individuals.

B. Results and Discussion

Presented below are currently available data, collected and analyzed to date, of variables which have been previously implied to be important in the occurrence of AMS. Some of the analyses are being performed by other laboratories and are not yet all available because these are best run in batch and will be performed when all studies are completed (e.g. catecholamines by Dr. Kamimori at Walter Reed and aldosterone, atrial natriuretic peptide, antidiuretic hormone and plasma renin by Dr. Hinghofer-Szalkay at the University of Graz, Austria). Fifty to 60% of these analyses have just been completed.

To date we have performed 81 complete experiments (altitude exposure/person). These include:

a) 18 male subjects (plus one repeated because of MRI malfunction)

b) 19 females during both menstrual phases and another 2 females in the follicular phase only. The latter could not be tested in the luteal phase because they were not available for another run.

c) 9 females taking oral contraceptives (OCP) studied twice, once at or near their pill week (highest progestin level) and once during their placebo week (lowest progestin level). Two of these also completed the menstrual cycle part of the study. One additional subject was tested during her pill week only and will not be repeated because of she is no longer available. Two

additional females have been tested during their placebo week and are scheduled for their pill runs. One more has completed her pill run. When this phase of the study is completed, we anticipate that 8 of the 18 placebo-pill pairs will be subjects who have also completed the menstrual cycle study portion of the study. All remaining subjects necessary to complete the study have been enrolled and scheduled and are in various stages of pre-testing.

The most pertinent and easily accessible data is presented below, along with some statistical comparisons between males and females and luteal (L) and follicular (F) phases in women. Some associations with AMS in subjects, independent of gender, menstrual phases or OCP's are also given. Only a small portion of the measurements listed in the appendix are available and most, except for the AMS scores, must be viewed as being preliminary, pending completion of more subjects, validation of measurements in individuals showing large deviations from the mean and application of other statistical methods.

Symptom Scores

We believe that in these 12-hr chamber exposures the subjects can and do exhibit true symptoms of AMS. When moderate or severe AMS developed during the 12-hr chamber exposure, significant AMS was still present following the MRI scan, approximately one hour after the subjects had been in a normal oxygen environment. The subjects are placed on a gas mixture containing 13% O_2 from the time that they leave the chamber until they enter the MRI facility. This transport time is approximately 15 min. A recent publication (2) has indicated that AMS symptoms occurring in an acute 9-hr chamber exposure are closely correlated with symptoms occurring in longer term exposure to true high altitude.

Males: Table 1A shows the age, VO_2max and Lake Louise AMS symptom scores obtained on the 18 men. Their mean age was 27 yr, the same as that of the women tested to date. Their VO_2max, measured on a ramp protocol on an exercise ergometer, was somewhat higher than the women, but all were above healthy sedentary values (3). The AMS scores show the expected variations among individuals and the increase with time at simulated altitude. Based on the minimum criterion of a total score 2, with a headache of 1, as indicating the presence of AMS (4), 12 of the 18 males had AMS (67%) and 6 did not. The table also shows the mean AMS score based on the values taken at hour 6 and the last hour. This is a valid estimate of AMS severity as it takes into account the time that AMS was present along with the peak value. The average (S.E.) of these mean scores is 3.53 (0.64), with an average peak headache score (highest value at hr 6 or last hr) of 1.7 (0.3).

Table 1A. Age, VO2max and Lake Louise symptom scores of 18 men.

Subj. #	Age	VO2max	A0	A1	A6	A12	Mean AMS	peak HA
0	26	45	**2**	4	3	8	5.5	3
1	31	55	**1**	**3**	5	7	6.0	2
3	26	50	0	0	0	0	0.0	0
5	22	32	0	0	**6**	9	7.5	3
7	31	52	0	0	2	3	2.5	2
9	29	40	0	0	5	7	6.0	2
10	28	39	0	**1**	6	11	8.5	3
12	20	46	0	**1**	3	5	4.0	2
14	28	54	0	0	0	1	0.5	1
15	26	59	0	**1**	0	1	0.5	1
17	24	31	0	1	3	**1**	2.0	1
19	27	49	0	0	**1**	0	0.5	0
20	31	43	0	0	**1**	**1**	1.0	0
22	32	48	0	0	3	5	4.0	3
24	26	50	0	3	5	6	5.5	2
25	22	37	0	0	**4**	7	5.5	2
27	28	51	0	**1**	0	0	0.0	0
28	27	57	0	0	2	6	4.0	3
Mean	27	46	0.2	0.8	2.7	4.3	3.53	1.7

A0: AMS score prior to entering chamber.

A1, A6, A12: AMS score at hour 1, 6, and 12 at altitude.

Bold: Headache score was zero.

VO2max: ml/min/kg

Table 1B. Age, VO2max, serum progesterone (ng/ml) and Lake Louise symptom scores of 21 women during follicular (F) and luteal (L) phase.

Subj. #	Age	VO2max	Prog	A0	A1	A6	A12	Mean AMS	peak HA
2F	33	33	0.3	0	0	**2**	3	2.5	1
2L			11.4	0	**1**	**1**	**1**	1.0	0
4F	26	33	0.3	0	1	3	1	2.0	1
4L			18.7	0	**1**	3	3	3.0	1
6F	27	36	0.4	0	0	1	3	2.0	2
6L			9.3	0	0	0	1	0.5	1
8F	24	37	0.2	0	0	**6**		6.0	0
8L			7.2	0	**1**	**5**	**5**	5.0	0
13F	32	32	0.3	**1**	**1**	2	2	2.0	1
13L			15.7	0	0	1	2	1.5	1
16F	27	36	0.4	**1**	0	**5**	4	4.5	1
16L			4.0	0	0	**2**	5	3.5	1
18F	22	45	0.5	0	0	**1**	**1**	1.0	0
18L			11.5	0	**1**	5	4	4.5	1
21F	23	48	0.7	0	**1**	3	4	3.5	2
21L			6.6	0	0	3	6	4.5	2
29F	28	34	0.4	0	0	1	1	1.0	1
29L			9.8	0	0	0	1	0.5	1
30F	26	29	0.4	0	0	**1**	4	2.5	2
30L			6.9	0	0	3	2	2.5	1
31F	27	48	0.3	**1**	1	1	2	1.5	1
31L			8.3	0	**1**	4	8	6.0	3
37F	24	52	0.3	0	0	4	4	4.0	1
37L			20.1	**1**	**4**	4	4	4.0	1
38F	27	37	0.4	0	**2**	4	11	7.5	3
38L			8.6	0	**4**	3	7	5.0	2
39F	28		0.4	0	4	8		8.0	2
39L			7.1	0	5	8	7	7.5	2
41F	32	28	0.4	0	0	0	**3**	1.5	0
41L			9.1	0	0	3	8	5.5	2
43F	21	47	0.5	0	0	3	2	2.5	2
43L			12.2	0	**2**	4	3	3.5	1
44F	28	27	0.3	**1**	**2**	3	10	6.5	3
44L			9.3	0	**1**	**4**	4	4.0	1
45F	32	46	0.2	0	0	6	12	9.0	3
45L			8.2	0	**2**	**5**	**6**	5.5	0
46F	22	38	0.4	0	0	**1**	4	2.5	1
46L			10.8	**1**	**1**	**2**	3	2.5	1
11F	32	33	0.2	0	0	**4**	3	3.5	1
11L									
23F	19	41	0.4	0	0	7	7	7.0	2
23L									
Mean F	27	38	0.3	0.2	0.6	3.1	4.3	3.83	1.4
Mean L	27	38	10.2	0.1	1.3	3.2	4.2	3.68	1.2

A0: AMS score prior to entering chamber.

A1, A6, A12: AMS score at hour 1, 6, and 12 at altitude.

Bold: Headache score was zero.

VO2max: ml/min/kg

Table 1C. Age, VO2max, serum progesterone (ng/ml) and Lake Louise symptom scores of 13 women on oral contraceptives during placebo (C) and pill (P) week.

Subj. #	Age	VO2max	Prog	A0	A1	A6	A12	Mean AMS	peak HA
4C	26	33	0.5	0	0	3	3	3.0	1
4P			0.3	0	0	3	3	3.0	2
16C	26	36	0.4	2	**2**	5	7	6.0	1
16P			0.4	0	0	**2**	**1**	1.5	0
32C	22	23	0.2	0	**2**	**4**	**1**	2.5	0
32P			0.3	0	**2**	3	4	3.5	2
33C	31	36	0.5	**2**	**2**	**1**	4	2.5	1
33P			0.4	**2**	**1**	7	7	7.0	2
34C	29	42	0.3	1	1	8	8	8.0	3
34P			2.4	0	**1**	3	3	3.0	1
35C	28	25	0.2	0	0	3	2	2.5	1
35P			0.3	0	1	**3**	3	3.0	1
36C	33	31	0.3	**1**	**1**	4	7	5.5	2
36P			0.2	0	0	**3**	5	4.0	2
40C	27	48	0.3	0	0	**2**	3	2.5	1
40P			0.3	0	**1**	**2**	5	3.5	1
42C	21	32	0.4	**1**	7	8	10	9.0	3
42P			0.5	2	**5**	**5**	6	5.5	3
26C	27	40							
26P			0.4	0	**1**	2	6	4.0	3
29C	28	34	0.2	0	0	0	2	1.0	1
29P									
47C	37	30							
47P			13.1	0	0	4	7	5.5	3
48C	20	34	0.4	0	**2**	10	9	9.5	3
48P									
Mean C	27	34	0.6	0.6	1.5	4.4	5.1	4.73	1.5
Mean P	27	34	0.8	0.4	1.1	3.4	4.5	3.95	1.8

A0: AMS score prior to entering chamber.

A1, A6, A12: AMS score at hour 1, 6, and 12 at altitude.

Bold: Headache score was zero.

VO2max: ml/min/kg

Women during follicular and luteal menstrual cycle phases: Nineteen women have been studied twice during the two menstrual phases. One of these subjects completed two runs on oral contraceptives prior to these tests. Eleven were studied first in the luteal phase (L) and 8 were studied first in the follicular phase (F). There was no significant order effect in these experiments, as a two-tailed t-test on the difference of the mean AMS scores between L and F gave a mean of 0.54 ($0.5<P>0.2$). Two additional women were studied only in the follicular phase. The results of the AMS scores are shown on table 1B. Fifteen of the 19 women (79%) had AMS during F by the above criteria and 14 of the 19 (74%) had AMS during L. In the 19 paired runs, the average LL AMS mean score in F was 3.68 (0.58), with a mean peak headache of 1.4 (0.2) and 3.68 (0.44) with a headache of 1.2 (0.2) in L. A significant correlation coefficient was found between the 19 pairs of mean AMS scores ($r = +0.56$, $P = 0.013$), indicating that AMS tended to be similar for the women in the two experiments. Therefore, based on this symptom-scoring criterion, there is no difference in AMS susceptibility between the two cycle phases. We anticipate that these results will be confirmed by results from the AMS-specific ESQ sub-scores when the compilation of these is completed. For the male subjects, for whom the AMS-C scores from the ESQ test have been compiled, the correlation with it and the mean LL AMS score was highly significant ($r = +0.88$, $P<0.01$). The average AMS mean score for each of the 19 women and the single value of the other two women in F gave an average mean score for all 21 of 3.83 (0.44).

Women on oral contraceptives: Nine paired runs are available for the two OCP runs (table1C). The average AMS mean score was 3.78 (0.53) during the pill run (P) and 4.61 (0.87) during the placebo (C) experiments. A paired comparison between these runs does not show statistical significance for this mean difference of 0.83 ($0.2>P<0.5$), but only half of the paired runs have been completed. Five of the subjects did P first and 4 did C first. No significant order effect is yet apparent, although the mean score was 1.34 higher during the first run. When the average mean score of these 9 women is combined with the 4 single runs (two C and two P), the average AMS mean score for the 13 OCP women is 4.44 (0.61). This value is higher, but not significantly different from that of the 3.84 for the menstrual cycle women ($0.2>P<0.5$). The two women who have, to date, completed both sets of runs show differences of less than 0.5 in their mean AMS scores. When the study is completed we hope to be able to compare paired measurements in 8 women from native and OCP-regulated cycles.

Males vs. females: The AMS score for the18 men (3.53) is not significantly different from the 3.83 obtained for the 21 women during menstrual phases (t = 0.39), nor is it different from the 4.44 obtained on the 13 women on OCP's (t = 0.93). Averaging all scores for each woman tested, regardless of phase, gave an average mean score of 4.22 for all 31 women. The difference between this value and that of the men also did not approach significance (0.2>P<0.5). Therefore, with tests to be completed on 9 remaining women, the preliminary results indicate that there is no significant difference between men and women in their susceptibility to AMS as measured by this instrument.

Ventilation

The total pulmonary ventilation (V_E), measured at rest over a 5-min period during the control period and after hr 1, 6 and during the last hr at altitude, are given in table 2A, B and C for the men, menstrual women and OCP subject groups, respectively.

Males: The 18 men had a mean resting V_E of 8.0 L/min during control conditions and a mean increase of 36% at altitude, based on the average of the three altitude measurements (table 2A). This percentage increase was not correlated significantly with their AMS scores (n = 18, r = -0.14, P = 0.58).

Women during follicular and luteal menstrual cycle phases: The mean control resting V_E was the same during F and L in the 19 paired studies (table 2B), indicating that the high endogenous progesterone during L did not alter baseline V_E. The increase in V_E with altitude exposure was seen in both groups and the mean increase was 9% greater in L. Although this higher V_E response was seen during L in 15 of the 19 women, this difference was not significant (paired t = 1.493, 0.1>P<0.2). The analyses of the acute hypoxic ventilatory response, as measured with the 3-breath nitrogen test is not yet available on a sufficient number of subjects for comparison. The mean V_E measured at altitude was significantly higher in L than in F (P<0.002). The increase in V_E as a response to altitude computed from all 40 runs from table 2B was also not significantly correlated with the AMS mean scores (r = 0.01, P = 0.95), similar to the observation in the males.

Women on oral contraceptives: The observations on table 2C are too few to make statistical observations. In general, it appears that the resting V_E and the increase in V_E with altitude is, so far, similar to those of the menstrual cycle women and the men.

Table 2A. Resting ventilation (L/min) of 18 men.

Subj. #	C12	A1	A6	A12	Δ%
0	10.5	13.7	11.6	10.4	13
1	5.1		8.1	9.9	76
3	8.0	14.3	16.1	17.6	101
5	8.2	10.4	10.6	10.7	29
7	7.4	11.1	11.5	9.3	45
9	9.4	12.8	13.2	13.1	39
10	9.2	11.4	12.3	14.9	40
12	9.4	10.3	10.7	12.8	21
14	7.8	10.7	10.8	9.6	33
15	8.4	11.7	13.9	16.1	66
17	7.5	8.8	9.2	8.5	18
19	8.3	7.8	11.3	7.4	7
20	7.2	9.2	9.1	8.2	22
22	8.5	10.6	13.7	10.3	36
24	7.4	8.1	6.9	7.1	-1
25	6.8	9.7	11.1	8.5	43
27	7.7	8.1	10.5	10.8	28
28	8.3	10.8	11.6	11.3	35
Mean	8.0	10.5	11.2	10.9	36

C12: Ventilation on control day.

A1, A6, A12: Ventilation at hour 1, 6 and 12 at altitude.

Δ%: Percent change of A1-A6 average from C12.

Table 2B. Resting ventilation (L/min) of 21 women.

Subj. #	C12	A1	A6	A12	Δ%
2F	9.2	12.0	12.9	12.1	34
2L	10.5	10.0	7.9	9.3	-13
4F	10.0	7.8	6.1	6.5	-32
4L	6.7	9.3	9.1	7.8	30
6F	7.1	7.6	6.7	8.7	7
6L	7.2	8.2	8.4	8.0	14
8F	7.3	8.0	9.6		20
8L	7.9	14.0	10.3		53
13F	8.1	7.1	9.1	8.0	0
13L	9.1	9.3	13.3	9.3	16
16F	5.5	7.4	6.2	7.3	26
16L	6.0	7.1	6.9	9.6	31
18F	5.9	7.8	11.0	9.3	58
18L	7.1	8.1	11.7	7.2	26
21F	8.2	7.9	8.3	9.1	2
21L	5.3	9.9	9.9	9.9	87
29F	9.4	8.8	8.8	8.1	-9
29L	6.5	8.5	9.1	8.0	31
30F	7.1	8.6	8.9	9.2	25
30L	7.2	10.0	10.3	8.4	33
31F	6.5	7.4	8.5	7.9	22
31L	7.1	9.0	8.7	9.5	29
37F	5.6	9.1	9.8	13.8	94
37L	7.5	10.8	13.5	10.4	54
38F	5.6	6.0	7.8	7.1	25
38L	5.8	6.4	7.1	8.6	27
39F	7.3	7.8	9.9		21
39L	8.5	8.2	8.9		0
41F	6.8	8.2	9.7	8.1	26
41L	6.6	9.4	9.6	9.4	44
43F	7.5	8.2	8.8	8.9	15
43L	8.2	9.3	10.5	10.0	20
44F	7.2	7.9	7.5	7.5	6
44L	8.7	9.5	9.6	10.4	13
45F	8.8	9.2	7.9	9.6	1
45L	6.7	8.1	7.6	8.4	20
46F	6.2	9.8	9.0	10.5	58
46L	5.1	8.2	12.5	8.8	93
11F	5.0	6.7	7.8	8.4	51
11L					
23F	5.6	7.8	7.2	6.0	26
23L					
Mean F	7.2	8.1	8.6	8.7	23
Mean L	7.2	9.1	9.7	9.0	32

C12: Ventilation on control day.

A1, A6, A12: Ventilation at hour 1, 6 and 12 at altitude.

Δ%: Percent change of A1-A6 average from C12.

Table 2C. Resting ventilation (L/min) of 13 women on oral contraceptives during placebo (C) and pill (P) week.

Subj. #	C12	A1	A6	A12	Δ%
4C	6.7	6.9	8.7	8.2	18
4P	6.9	6.9	8.4	8.9	16
16C	6.4	7.5	8.7	7.3	22
16P	6.4	6.7	7.8	7.0	12
32C					
32P	7.8	8.6	6.5	7.9	-1
33C					
33P	6.6	13.4	11.4	11.8	86
34C	7.7				
34P					
35C					
35P	7.3	8.5	9.4	7.0	13
36C	8.3	10.0	10.0	9.9	20
36P	8.3	10.6	10.9	9.8	27
40C					
40P					
42C					
42P					
26C					
26P					
29C					
29P					
47C					
47P					
48C					
48P					
Mean C	7.3	8.1	9.2	8.4	20
Mean P	7.2	9.1	9.1	8.7	26

C12: Ventilation on control day.

A1, A6, A12: Ventilation at hour 1, 6 and 12 at altitude.

Δ%: Percent change of A1-A6 average from C12.

Arterial blood gases

Males: The arterial blood pH increased significantly from hour 1 to 12 at simulated altitude by an average of 0.026 pH units (table 3A). The PCO_2 fell by almost 5 mm Hg, although the total ventilation remained about the same. The decrease in base excess calculated from these values (5) is 1.2 mEq/L over the 10 hours, indicating the active elimination of bicarbonate by the kidneys over this relatively short time at altitude. The arterial PO_2 remained unchanged over this time as the O_2 saturation was about 82%. Table 3A also shows the change in the end-tidal (alveolar) - to - arterial PO_2 difference measured from the first to the 12th hour. The mean difference increased only about 1 mm Hg, indicating no appreciable decline in gas exchange efficiency. The development of diffusion impairment or right–to-left shunt would be expected to increase the PO_2 difference at A12 relative to A1. The arterial - alveolar PCO_2 difference also showed little change during the altitude exposure. This demonstrates that there was no increase in ventilation/perfusion mismatch over time at altitude. There was no correlation between either of these alveolar - arterial differences and AMS symptom scores. The PaO_2 at A12 also did not show a significant relationship with AMS scores ($r = -0.20$, $P = 0.42$), showing that the degree of hypoxemia was not clearly associated with symptom development in susceptible individuals.

Women during follicular and luteal menstrual cycle phases: The blood gas values on table3B are very similar to those of the men and the changes from hour 1 to hour 12 were also similar. The differences between F and L noted at the bottom of the table were very small and not significant. In this group there was also no significant correlation between the AMS mean score and PaO_2 at A12 or the change in the alveolar – arterial differences during the time at altitude.

Women on oral contraceptives: These studies are still incomplete (table3C), but the mean values are similar to the menstrual cycle women.

Body water

Males: The analyses for the completed runs have not all been performed because they are done at a commercial laboratory and are sent and analyzed periodically in batch. From the values in Table 4A, it is apparent that the average A12 values for extracellular water (ECW) are increased at altitude from the preceding control day. An increase in ECW is indicative of general tissue edema and is often thought to be related to AMS severity. The ECW correlated

Table 3A. Arterial blood gas values of 18 men during the 2nd and 12th hr (A1, A12) at altitude.

	A1			A12				
Subj. #	Pha	PaO2	PaCO2	Pha	PaO2	PaCO2	ΔPO2	ΔPCO2
0	7.450	48.4	36.1	7.496	52.7	28.3	-2.8	-9.7
1				7.520	47.0	26.0		
3	7.420	51.3	32.0	7.440	52.5	30.0	1.9	-1.4
5	7.415	49.0	31.5	7.435	47.5	29.5	1.2	1.3
7	7.435	47.0	36.5	7.450	42.5	33.5	2.7	-1.7
9	7.410	42.0	40.0	7.455	38.5	34.5	4.7	-2
10	7.432	41.3	38.4	7.459	40.8	31.6	5.8	-1.1
12	7.443	43.3	34.1	7.479	48.7	28.5	-0.5	0.2
14	7.435	41.2	38.2	7.465	38.2	33.4	2.2	-2.2
15	7.471	47.2	32.8	7.445	45.0	33.1	2.2	1.1
17	7.446	44.3	39.0	7.467	43.3	33.1	0.8	-2.3
19	7.466	42.9	32.5	7.466	41.2	31.1	1.2	-0.1
20	7.461	52.2	35.7	7.506	42.9	28.2	5.3	1.1
22	7.444	43.2	36.6	7.458	42.4	32.5	2.5	-0.6
24	7.472	35.9	36.0	7.469	35.4	33.1	0.7	-0.8
25	7.456	39.1	36.3	7.495	42.3	28.9	0.1	-2.4
27	7.444	43.5	34.3	7.489	54.6	29.3	-8.1	-4.5
28	7.451	39.3	37.7	7.467	35.6	34.3	2	0.6
Mean	7.444	44.2	35.7	7.470	44.0	31.1	1.3	-1.4

ΔPO2: End-tidal minus arterial PO2 difference at A12 minus difference at A1.

ΔPCO2: Arterial minus end-tidal PCO2 difference at A12 minus difference at A1.

Table 3B. Arterial blood gas values of 21 women during the 2nd and 12th hr (A1, A12) at altitude.

	A1			A12				
Subj. #	Pha	PaO2	PaCO2	Pha	PaO2	PaCO2	ΔPO2	ΔPCO2
2F	7.440	50.0	36.0	7.465	50.5	31.5	1.7	-3.1
2L	7.440	43.0	29.0	7.465	47.5	26.0	-3.7	-2.2
4F	7.430	44.0	35.5	7.470	48.5	30.0	-8.4	-6.3
4L	7.430	45.0	30.0	7.450	49.0	25.0	-1.9	0.2
6F	7.465	52.0	31.0	7.495	63.5	25.0	-4.1	-1.4
6L	7.475	49.9	29.4	7.467	40.8	29.5	3.7	1.2
8F	7.436	39.3	37.5	7.466	37.2	32.0		
8L	7.445	42.5	35.0	7.450	39.0	32.0	5.8	1.5
13F	7.470	40.8	33.6	7.563	45.4	28.0	2.1	-0.7
13L	7.481	44.1	29.4	7.525	47.1	24.1	-1.1	-1.8
16F	7.417	43.6	37.3	7.449	40.1	32.2	4.1	-1.7
16L	7.435	41.0	34.7	7.454	40.5	32.2	2.0	-0.1
18F	7.435	44.8	32.1	7.445	46.3	31.9	2.1	-0.7
18L	7.444	45.9	29.9					
21F	7.436	40.3	34.7	7.437	39.4	32.3	-1.5	0.1
21L	7.441	48.5	34.9	7.434	45.0	31.8	1.2	1.9
29F	7.474	44.3	32.0	7.476	40.3	30.1	-0.8	-1.9
29L	7.458	43.0	31.2	7.473	40.1	28.2	1.2	1.2
30F								
30L	7.454	43.8	33.3	7.466	38.7	29.8	4.9	0.9
31F	7.429	42.7	31.3	7.462	42.4	27.4	2.1	-0.6
31L	7.431	50.4	29.5	7.466	50.0	25.4	1.0	-0.1
37F	7.477	48.5	30.8	7.562	57.4	20.2	4.4	-0.1
37L	7.474	39.6	30.1	7.461	41.8	29.0	-2.5	0.8
38F	7.410	36.0	38.0	7.446	38.8	29.6	-6.7	-9.6
38L	7.472	45.5	30.1	7.522	43.7	24.7	8.1	3.5
39F	7.400	56.0	30.0	7.478	42	27.7	18.8	5.3
39L	7.474	41.6	28.5	7.487	44.1	25.7	-1.7	-1.2
41F	7.440	46.4	32.7	7.450	38.6	29.7		
41L	7.426	41.1	33.2	7.475	40.4	26.2	1.2	0.4
43F	7.468	44.3	32.3	7.476	43.6	28.1	2.9	-0.1
43L	7.464	41.9	28.6	7.452	42.0	27.4	3.1	1.1
44F	7.487	39.3	34.1	7.486	39.3	28.9	2.3	-0.4
44L	7.472	39.4	32.0	7.483	40.1	25.8	1.9	-1
45F								
45L	7.469	42.5	33.2	7.490	39.0	26.8	1.2	0.3
46F	7.478	48.7	30.5	7.485	44.8	27.9	5.0	0.6
46L	7.474	41.4	32.4	7.450	37.0	30.0	9.6	3.8
11F	7.462	48.8	34.0	7.466	46.2	32.6	4.7	1.1
11L								
23F	7.434	45.5	32.1	7.448	45.6	29.1	-0.9	-0.1
23L								
Mean F	7.447	45.0	33.4	7.475	44.7	29.2	1.6	-1.2
Mean L	7.456	43.7	31.3	7.471	42.5	27.8	1.9	0.6

ΔPO2: End-tidal minus arterial PO2 difference at A12 minus difference at A1.

ΔPCO2: Arterial minus end-tidal PCO2 difference at A12 minus difference at A1.

Table 3C. Arterial blood gas values of 13 women on oral contraceptives during the 2nd and 12th hr (A1, A12) at altitude.

	A1			A12				
Subj. #	Pha	PaO2	PaCO2	Pha	PaO2	PaCO2	ΔPO2	ΔPCO2
4C	7.467	46.0	30.0	7.479	46.4	26.3	2.2	1.8
4P								
16C	7.441	42.9	35.0	7.450	41.8	30.7	1.1	-0.1
16P	7.415	43.5	35.2	7.450	42.5	29.1	2.3	-3.3
32C	7.437	45.9	34.1	7.460	43.4	31.9		
32P	7.447	44.0	32.4	7.440	41.4	31.5	1.4	-0.6
33C	7.474	44.6	29.5	7.515	42.1	24.9		
33P								
34C	7.445	38.4	35.6	7.453	40.9	31.8		
34P								
35C	7.418	48.4	31.1	7.457	44.4	28.0		
35P	7.459	48.4	28.4	7.441	42.9	27.9	4.5	0.5
36C	7.437	43.3	32.5	7.459	45.1	29.6	-0.1	1.7
36P	7.443	44.7	30.5	7.464	39.9	28.4	2.6	0.9
40C								
40P								
42C	7.469	32.9	37.1					
42P	7.456	35.2	33.8	7.477	38.7	31.2		
26C								
26P	7.523	50.3	24.5	7.540	52.1	21.0	4.8	0.3
29C								
29P								
47C								
47P								
48C								
48P								
Mean C	7.449	42.8	33.1	7.468	43.4	29.0	1.1	1.1
Mean P	7.457	44.4	30.8	7.469	42.9	28.2	3.1	-0.4

ΔPO2: End-tidal minus arterial PO2 difference at A12 minus difference at A1.

ΔPCO2: Arterial minus end-tidal PCO2 difference at A12 minus difference at A1.

Table 4A. (a) Extracellular water (L) and (b) total body water (Kg) on control day and during A12 at altitude in 18 men.

(a)

Extracellular water (L)			
Subj. #	C12	A12	Δ%
0	15.7	15.8	1.0
1	15.8	16.6	4.8
3	18.6	18.3	-1.1
5	18.6	29.1	57.0
7	15.5	13.8	-10.9
9	18.9	30.6	62.3
10	16.1	N	
12	18.8	20.3	8.0
14	18.7	18.5	-1.4
15	14.9	13.6	-8.9
17	16.5	16.1	-2.5
19	16.3	15.5	-5.0
20	13.8	14.3	3.3
22	18.1	29.7	64.0
24	12.9	13.5	4.5
25	17.7	18.2	2.8
27	13.6	12.6	-7.2
28	19.6	30.9	57.7
Mean	16.7	19.3	13.4

N: Not available because of vomiting.

(b)

Total Body water (Kg)			
Subj. #	C12	A12	Δ%
0	50.3	45.8	-8.9
1	46	44	-4.3
3	50.5	46.9	-7.1
5	50.6	57.1	12.8
7	44.2	44.7	1.1
9	58	56.8	-2.1
10	50.5	N	
12	54.5	55	0.9
14	55.1	52.8	-4.2
15	42.2	42	-0.5
17	49.6	45.7	-7.9
19	49.7	48.6	-2.2
20	38.6	38.4	-0.5
22	52.6	55.7	5.9
24	38	42.7	12.4
25	46.9	43.1	-8.1
27	42.9	42.1	-1.9
28	57.7	63.6	10.2
Mean	48.8	48.5	-0.3

Table 4B. (a) Extracellular water (L) and (b) total body water (Kg) on control day and during A12 at altitude in 21 women.

(a) Extracellular water (L)			
Subj. #	C12	A12	Δ%
2F	14.6	14.5	-1.0
2L	14.0	13.3	-5.1
4F	9.3	10.1	7.7
4L	9.2	8.8	-4.7
6F	9.7	11.7	20.5
6L	10.7	10.4	-3.0
8F	14.9	N	
8L	16.3	N	
13F	11.6	12.2	4.5
13L	11.2	10.7	-4.9
16F			
16L			
18F	12.5	13.4	6.9
18L	13.4	11.9	-11.2
21F	15.8	N	
21L	13.8	N	
29F	14.8	14.4	-2.2
29L			
30F	17.7	19.7	11.1
30L	16.4	15.8	-3.3
31F	12.6	13.0	3.6
31L	11.0	21.8	98.4
37F	13.3	13.2	-0.9
37L	11.9	12.9	8.5
38F	11.6	N	
38L			
39F	15.2	N	
39L			
41F	13.1	15.3	16.5
41L	16.4	N	
43F			
43L			
44F			
44L			
45F			
45L			
46F			
46L			
11F	12.7	12.4	-2.2
11L			
23F	11.4	13.3	17.2
23L			
Mean F	13.2	13.6	6.8
Mean L	13.1	13.2	9.3

(b) Total Body water (Kg)			
Subj. #	C12	A12	Δ%
2F	37.5	35.8	-4.5
2L	36.6	38.2	4.4
4F	25	24.2	-3.2
4L	24.9	23.7	-4.8
6F	27.5	28.2	2.5
6L	28.2	29.0	2.8
8F	39.9	N	
8L	44.4	N	
13F	31.6	32.6	3.2
13L	29.8	30.0	0.7
16F			
16L			
18F	33.2	33.3	0.3
18L	32.8	40.6	23.8
21F	41.3	N	
21L	38.6	N	
29F	41.5	37	-10.8
29L			
30F	41.4	50.6	22.2
30L	42.1	44.2	5.0
31F	33	28	-15.2
31L	30.2	35.8	18.5
37F	35.9	35.6	-0.8
37L	33.9	34.8	2.7
38F	30	N	
38L			
39F	33.3	N	
39L			
41F	34.6	33	-4.6
41L	37.0	N	
43F			
43L			
44F			
44L			
45F			
45L			
46F			
46L			
11F	33.7	33.4	-0.9
11L			
23F	29.3	33.3	13.7
23L			
Mean F	34.3	33.8	0.2
Mean L	34.4	34.5	6.6

N: Not available because of vomiting.

Table 4C. (a) Extracellular water (L) and (b) total body water (Kg) on control day and during A12 at altitude in OCP women.

(a)

Extracellular water (L)			
Subj. #	C12	A12	Δ%
4C	9.2	8.8	-4.3
4P	8.6	N	
16C	9.4	N	
16P	10.2	9.3	-8.9
32C			
32P	15.4	17.4	12.6
33C	14.6	16.6	13.6
33P	14.0	12.7	-9.4
34C	12.0	N	
34P			
35C			
35P	9.0	10.1	11.9
36C	10.4	13.7	31.6
36P	10.2	11.1	9.3
40C			
40P	11.5	11.8	2.8
42C	20.0	12.4	-38.0
42P			
26C			
26P			
29C			
29P			
47C			
47P			
48C			
48P			
Mean C	12.6	12.9	0.7
Mean P	11.3	12.0	3.0

N: Not available because of vomiting.

(b)

Total Body water (Kg)			
Subj. #	C12	A12	Δ%
4C	24.7	24.3	-1.6
4P	23	N	
16C	28.5	N	
16P	28	25.2	-10.0
32C			
32P	37.6	39.8	5.9
33C	36.4	37.7	3.6
33P	40.1	44.5	11.0
34C	33.9	N	
34P			
35C			
35P	27.1	25.7	-5.2
36C	29.3	34.5	17.7
36P	29	28.3	-2.4
40C			
40P	29	26.2	-9.7
42C	33.5	36.7	9.6
42P			
26C			
26P			
29C			
29P			
47C			
47P			
48C			
48P			
Mean C	31.1	33.3	7.3
Mean P	30.5	31.6	-1.7

significantly with the AMS mean scores (r = +0.563, P = 0.019). A few of the values shown in this table at A12 are obviously too large to be physiological and it is possible that the absorption and mixing of the NaBr is affected by altitude to result in these spurious values. The average AMS mean score for the 10 men who showed an increase in ECW at altitude is 4.9 and the average of the 7 who had a negative change was 0.9 (P<0.002). The mean change in TBW with altitude exposure was negligible, however the correlation between the percent change and AMS mean score approached statistical significance suggesting that TBW increased with AMS and decreased in those subjects not experiencing AMS. The difference between these two measures is intracellular water (ICW), which gave an average decline of 7%. These percent changes in ICW were not significantly correlated with AMS scores.

Women: The number of values are too limited to attempt to differentiate between the two groups and subgroups of women (tables 4B and C). Considering all women together, the correlation with mean AMS score was not significant with ECW. However the TBW was significantly correlated with AMS mean score (r = +0.55, P = 0.002, n = 30).

Combining all men and women with the data currently available, both the percent changes in ECW and TBW at altitude, relative to control, correlate positively with AMS mean score (r = +0.30, P = 0.038 and r = +0.46, P = 0.001, respectively, n = 47).

Urine Volume

In order to estimate the general trend of urine volume occurring over time at altitude we computed the percentage change in the volume averaged for the last two collection intervals (A9 and A12) relative to the average of the first collection at altitude and the collection on the control day. A decreased urine volume is typically expected in subjects experiencing AMS and a diuresis is considered to be a beneficial response to acute altitude (6).

Males: The mean decline in the men was 39% (table 5A). The correlation between the urine volume and mean AMS score was in the direction expected, but not significant (r = -0.16).

Women during follicular and luteal menstrual cycle phases

About the same average decline was seen in the menstrual cycle group of women and there was no apparent difference between L and F (table 5B). The diuresis was not related to mean AMS symptom score in F or L separately, giving r = -0.35 and -0.36, respectively, but combining all 40 subjects resulted in a significant r value of -0.34 (P = 0.03).

Table 5A. Urine volume (ml/hr) of 18 men 12 hr before (C12) and after 3, 6, 9 and 12 hr of altitude exposure.

Subj. #	C12	A3	A6	A9	A12	Δ%
0	207	303.3	333.3	380	238	21
1	893	580	105	215	147	-75
3	141	443	552	182	271	-22
5	358	382	65	86	200	-61
7	151	387	491	259	293	3
9	775	230	78	103	355	-54
10	173	303	232	68	68	-71
12	409	341	389	289	239	-30
14	683	474	129	305	51	-69
15	259	227	79	308	266	18
17	426	722	413	179	187	-68
19	523	526	482	282	257	-49
20	235	325	127	79	32	-80
22	244	142	326	203	394	55
24	422	123	338	141	129	-50
25	358	324	406	221	105	-52
27	363	585	581	372	249	-34
28	220	209	100	54	58	-74
Mean	380	368	290	207	197	-39

Δ%: Percent change of A9 and A12 average from C12 and A3 average.

Table 5B. Urine volume (ml/hr) of 21 women 12 hr before (C12) and after 3, 6, 9 and 12 hr of altitude exposure.

Subj. #	C12	A3	A6	A9	A12	Δ%
2F	564	393	415	336	369	-26
2L	330	431	697	361	558	21
4F	110	200	49	23	47	-77
4L	186	163	62	8	140	-58
6F	341	621	293	415	79	-49
6L	226	532	277	183	171	-53
8F	182	391	141	0		-100
8L	533	352	0	0		-100
13F	221	299	513	158	315	-9
13L	265	423	397	416	477	30
16F	188	133	58	44	191	-27
16L	101	240	208	183	128	-9
18F	103	312	126	194	185	-9
18L	130	349	436	265	416	42
21F	103	235	0	89	0	-74
21L	466	637	245	0	25	-98
29F	434	490	160	427	192	-33
29L	311	317	227	61	213	-56
30F	561	560	589	385	249	-43
30L	365	281	710	523	616	76
31F	688	425	522	286	197	-57
31L	333	420	580	131	38	-78
37F	166	134	190	270	312	94
37L	95	308	210	249	191	9
38F	357	70	56	33		-85
38L	60	252	243	91		-42
39F	428	107	55	55		-79
39L	151	233	300	146		-24
41F	398	624	791	406	200	-41
41L	272	561	349	0	0	-100
43F	893	356	271	56	172	-82
43L	123	298	308	53	337	-7
44F	187	183	217	67	187	-31
44L	184	463	104	174	153	-49
45F	441	411	342	50	41	-89
45L	201	385	118	50	64	-81
46F	173	263	266	457	153	40
46L	230	242	521	230	114	-27
11F	180	211	167	164	210	-4
11L						
23F	344	278	111	153	209	-42
23L						
Mean F	336	319	254	194	184	-39
Mean L	240	362	315	164	228	-32

Δ%: Percent change of A9 and A12 average from C12 and A3 average.

Table 5C. Urine volume (ml/hr) of 13 OCP women 12 hr before (C12) and after 3, 6, 9 and 12 hr of altitude exposure.

Subj. #	C12	A3	A6	A9	A12	Δ%
4C	239	289	29	42	62	-80
4P	163	237	137	80	90	-58
16C	403	256	49	49	40	-86
16P	454	577	279	71	325	-62
32C	106	309	312	217	161	-9
32P	214	242	121	185	181	-20
33C	113	423	850	1209	290	180
33P	290	168	765	637	575	165
34C	142	283	42	16		-92
34P	31	204	185	171		46
35C	100	233	249	227	64	-13
35P	249	322	294	127	198	-43
36C	201	360	179	56	55	-80
36P	118	386	151	328	176	0
40C	44	183	57	140	76	-5
40P	443	76	99	38	38	-85
42C	198	101	389	154	78	-22
42P	180	73	170	187	49	-7
26C						
26P						
29C						
29P						
47C						
47P						
48C						
48P						
Mean C	172	271	240	234	103	-23
Mean P	238	254	244	203	204	-7

Δ%: Percent change of A9 and A12 average from C12 and A3 average.

Women on oral contraceptives

The mean percent decline in urine volume at altitude was smaller in these women (table 5C) than in women not taking OCP's. The urine volume at altitude in the P group declined less than in the placebo (C) group and they also had a lower AMS mean score. A negative, but not significant correlation ($r = -0.54$) was noted between percentage reduction in urine volume and the AMS mean score in C, but a significant positive correlation was noted in the same 9 subjects during P.

Plasma volume:

Males: The plasma volume (PV) values were measured with Evans blue dye. These values were obtained from zero-time extrapolation of a 3-hr decay curve of dye injected at the same time of day on the control day and after 9 hours at altitude. Samples were taken at 10, 20, 30, 60, 120 and 180 minutes after injection of 12 mg of dye. On the average the PV was 3% lower at altitude than during C12, showing a large scatter. The percentage change in PV was insignificantly correlated with the AMS score ($r = 0.28$, $P = 0.28$).

Women: The average reduction in PV was about twice as large as for the men and about the same in F and L. The correlation coeficient with AMS was only 0.19 for all 40 women not on the pill. The women on OCP averaged about the same as the men, but there was essentually no change in P. There correlation with AMS was also not significant, but it was negative ($r = -0.37$) for the 18 paired runs shown in table 6C.

In our last report, based on very few subjects, we noted a significant positive correlation between PV and AMS score, suggesting that a reduction in PV at altitude was beneficial. With the additional subjects we have tested to date, the significant correlation is no longer present. This discrepancy may also be related to the fact that some of the subjects with more severe AMS vomit towards the end of the chamber exposure and thereby decrease their PV, making their measurements appear like those in altitude-tolerant subjects.

Transcapillary escape rate (TCER)

These values, as determined from the decay slope of the Evans Blue dye over 3 hours, are also shown in tables 6A, B and C. The values are expressed as the percentage change in dye concentration per hour, which is representative of the rate of albumin loss from the vascular space. Overall, the TCER was smaller by 1.3% at altitude than on the corresponding

Table 6A. (a) Plasma volume (ml) and (b) transcapillary escape rate (%/hr) on control day and during A12 at altitude in 18 men.

(a)

Subj. #	C12	A12	Δ%
0	3551	4044	13.9
1	3311	3501	5.7
3	5226	4679	-10.5
5	3761	4046	7.6
7	4266	4181	-2.0
9	3819	4296	12.5
10	3528	N	
12	4268	4227	-1.0
14	5037	4457	-11.5
15	3959	4346	9.8
17	3588	3732	4.0
19	4498	3949	-12.2
20	4104	3673	-10.5
22	4871	4311	-11.5
24	3252	3357	3.2
25	4783	3082	-35.6
27	3412	3216	-5.7
28	4242	3923	-7.5
Mean	4082	3942	-3

N: Not measured.

(b)

Subj. #	C12	A12	Diff.
0	-6.8	-11.8	-5.0
1	-0.1	-7.8	-7.7
3	-1.8	-1.5	0.3
5	0.7	-2.6	-3.3
7	-14.5	-8.0	6.5
9	-9.0	-8.3	0.7
10	-5.5	N	
12	-7.2	-5.1	2.1
14	-5.8	-8.0	-2.2
15	-2.5	-14.8	-12.3
17	-6.7	-6.8	-0.1
19	-3	-5.8	-2.8
20	-14.2	-5.6	8.6
22	-10.5	-9	1.5
24	-4.2	6.8	11.0
25	-24.7	-11.6	13.1
27	-7.8	-8.2	-0.4
28	-21.4	-9	12.4
Mean	-8.1	-6.9	1.3

Table 6B. (a) Plasma volume (ml) and (b) transcapillary escape rate (%/hr) on control day and during A12 at altitude in 21 women.

(a)

Subj. #	C12	A12	Δ%
2F	3327	3492	5.0
2L	3518	2894	-17.7
4F	2080	1993	-4.2
4L	2210	1995	-9.7
6F	2527	2488	-1.5
6L	2674	2121	-20.7
8F	4405	3306	-24.9
8L	4294	4510	5.0
13F	2762	2366	-14.3
13L	2975	2740	-7.9
16F	2718	2354	-13.4
16L	3426	2793	-18.5
18F	3845	2865	-25.5
18L	3582	3049	-14.9
21F	4052	3912	-3.5
21L	3291	3813	15.9
29F	3718	3545	-4.7
29L	3768	3728	-1.1
30F	4717	4262	-9.6
30L	4235	4219	-0.4
31F	3037	3103	2.2
31L	2676	3005	12.3
37F	3377	3242	-4.0
37L	3571	3249	-9.0
38F	2995	2920	-2.5
38L	3321	2853	-14.1
39F	2839	2629	-7.4
39L	3792	2849	-24.9
41F	3481	2872	-17.5
41L	3052	3170	3.9
43F	3653	3244	-11.2
43L	3177	3042	-4.2
44F	3479	3167	-9.0
44L	3632	3006	-17.2
45F	3265	3225	-1.2
45L	3537	3069	-13.2
46F	3685	2684	-27.2
46L	3167	2718	-14.2
11F	3219	2895	-10.1
11L			
23F	2600	2805	7.9
23L			
Mean F	3323	3018	-8.4
Mean L	3363	3096	-7.9

(b)

Subj. #	C12	A12	Diff.
2F	-7.5	-3.8	3.7
2L	-5.6	-12.8	-7.2
4F	-10.2	-8.4	1.8
4L	-4.4	-6.4	-2.0
6F	-4.9	-1.5	3.4
6L	-0.7	-10.2	-9.5
8F	-7.4	-11.9	-4.5
8L	-4.7	N	
13F	-9.4	-9.1	0.3
13L	-7	-4.5	2.5
16F	-6.4	-2.2	4.2
16L	5.1	-15.5	-20.6
18F	-7.5	-8.4	-0.9
18L	-4.6	-5.4	-0.8
21F	-3.6	1.7	5.3
21L	-6.8	-2.8	4.0
29F	-4	-2.2	1.8
29L	-4.4	-2.3	2.1
30F	0.1	-5.4	-5.5
30L	-5.4	-0.7	4.7
31F	-9.9	-1.1	8.8
31L	-8.4	-2.8	5.6
37F	-6.8	-7	-0.2
37L	-4.9	-6	-1.1
38F	-3.4	16.9	20.3
38L	7.4	2	-5.4
39F	-6.5	N	
39L	-1.2	-14.6	-13.4
41F	-5.3	-9.6	-4.3
41L	-9	N	
43F	-7.5	-6.5	1.0
43L	-5.3	-9.3	-4.0
44F	-4.6	-6.9	-2.3
44L	-4.3	-8.4	-4.1
45F	-4.4	-6.5	-2.1
45L	-2	-2.4	-0.4
46F	-13.8	-3.4	10.4
46L	-15.5	-10.9	4.6
11F	-0.5	0.8	1.3
11L			
23F	-7.2	0.9	8.1
23L			
Mean F	-6.2	-3.7	2.5
Mean L	-4.3	-6.6	-2.6

N: Not sufficient samples for valid decay slope.

Table 6C. (a) Plasma volume (ml) and (b) transcapillary escape rate (%/hr) on control day and during A12 at altitude in 13 OCP women.

(a)

Subj. #	C12	A12	Δ%
4C	2174	2090	-3.9
4P	2487	2182	-12.3
16C	2557	2547	-0.4
16P	2803	2587	-7.7
32C	3378	3175	-6.0
32P	3477	3744	7.7
33C	3780	3820	1.1
33P	3612	3276	-9.3
34C	3104	2848	-8.2
34P	2597	2548	-1.9
35C	2435	2557	5.0
35P	2372	2296	-3.2
36C	3335	2967	-11.0
36P	2904	2764	-4.8
40C	3021	2733	-9.5
40P	3155	3973	25.9
42C	3208	2570	-19.9
42P	2882	2822	-2.1
26C			
26P			
29C			
29P			
47C			
47P			
48C			
48P			
Mean C	2999	2812	-5.9
Mean P	2921	2910	-0.9

(b)

Subj. #	C12	A12	Diff.
4C	-5.6	-7.8	-2.2
4P	-7.1	-5.6	1.5
16C	-5.8	-2.1	3.7
16P	-8.8	-4.6	4.2
32C	-0.9	-11.1	-10.2
32P	-4.7	2.3	7.0
33C	-4.4	-5.5	-1.1
33P	-5.8	-6.7	-0.9
34C	-7.8	N	
34P	-9.8	-12.7	-2.9
35C	-0.3	-3.5	-3.2
35P	-3.4	-1.2	2.2
36C	-5.2	-8.3	-3.1
36P	-7.3	-6.1	1.2
40C	-6.3	-7.3	-1.0
40P	-3.5	9.8	13.3
42C	0	-8.2	-8.2
42P	-5.2	-6.4	-1.2
26C			
26P			
29C			
29P			
47C			
47P			
48C			
48P			
Mean C	-4.0	-6.7	-3.2
Mean P	-6.2	-3.5	2.7

N: Not sufficient samples for valid decay slope.

control day for the men. It was also smaller at altitude during the follicular and pill runs, but showed the reverse trend in the other two women subgroups. No significant correlations were found between the change in TCER and the AMS scores in any of the subgroups or all 71 runs combined. The mean change at altitude for all 71 runs was 0.34%, indicating that altitude does not increase TCER, as suggested previously (7). If altitude did increase TCER, a negative number significantly less than zero should have been seen.

Magnetic Resonance Imaging (MRI) data collection and analyses

All MRI scans to date have been evaluated by a licenced neuroradiologist for structural abnormalities that are considered clinically significant and for qualitative evidence of cerebral edema. None of the subjects have exhibited any abnormalities that could be construed as having resulted from the exposures to hypoxia and all the findings noted have been categorized as being within the recognized deviations of normal. It remains to be seen whether the more quantitative analyses of the images now in progress will uncover any control-post altitude differences that will show any correlation with the degree of AMS (headache, nausea, dizziness, fatigue) seen in the subjects. AMS symptoms have ranged from none to a maximum score of 12 on the LL scoring tool and occasionally the chamber exposures have been less than 12 hours because of the severity of AMS.

Every subject has undergone MRI at the end of the control day and at the end of the altitude chamber day. The MRI data collected include: a) T1 weighted 3-D data set, b) T2 weighted series of image slices through the cerebellum and cerebrum, c) Magnetization Transfer Contrast (MTC) slice series and d) Diffusion weighted slice series.

The T1 weighted 3-D data set is used to orient the slice selection so that the slices match on the control and post altitude studies. This data set is also being analyzed to evaluate the brain for any changes in tissue volume, as detailed in the last report. The 2-D images from the 3-D set are manually segmented into the cerebellum, brainstem above the first cervical vertebrae and cerebellum. Using a consistent signal threshold in each pixel, the pixels are identified as tissue or non-tissue for each region. The tissue volume is calculated by counting the pixels from all of the 2-D images in the 3-D dataset from each segmented region of the brain. The parts of the analysis that are operator-dependent have the operator blinded to which part of the protocol the images came from.

The T2 weighted, MTC and Diffusion weighted images are placed and oriented in the same region of the brain for each study by localizing the slices using landmarks from the 3-D T1 data set. This allows subtraction of these images for data analysis. Due to minor

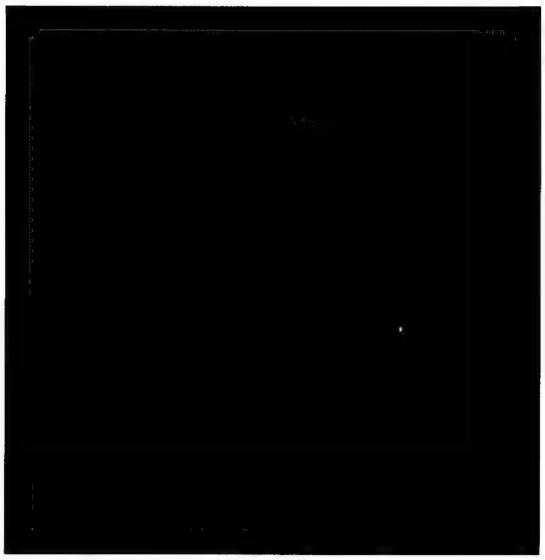
localization differences, brain pulsatility, and subject motion, the image margins are of limited use. However, as little as a 3 to 5% signal difference in larger tissue regions is quite evident after image subtraction.

CSF Volume Measurements: Our objective is to determine whether there is a significant change in brain CSF volume between images taken on the control day and after the high altitude exposure. The MRI experiment was done in a Picker 1.5T whole body magnet. CSF volume was calculated from 20, T2 weighted, 5 mm thick slices. CSF is characterized by long T2 values and it appears bright in long echo time images. Gray matter appears darker and white matter is even darker. A multi-slice, four echo pulse sequence was used for imaging. The echo times were 30, 60, 90, and 120 ms, the FOV view was 29.5 cm, and the image size was 256 x 256 giving a resolution of 1.152 mm.

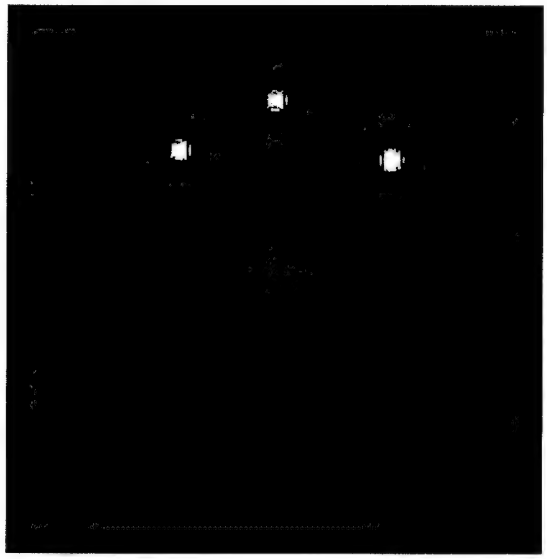
CSF was calculated from a normalized image, consisting of a ratio of long to short echo time images. If I_{30} is the image at an echo time of 30 ms and I_{120} is the image at an echo time of 120 ms, the normalized image is defined by $N = I_{120}/I_{30}$. The normalization compensates for variations in proton density and any other systematic variation in signal intensity.

Normalized images were examined manually and mean signal intensity values were calculated in three regions: a) 100 % CSF, b) region of lowest intensity where CSF could be visually detected, and c) gray matter region. The mean values of the normalized intensities in these three regions were: 100 % CSF - mean = 0.77, Minimum detectable CSF region - mean = 0.32, and gray matter region - mean = 0.24. We considered a possible candidate for CSF as any voxel having an intensity above 0.32. These regions were marked automatically for the whole 3D data set. The next step consisted of manually eliminating the regions that were clearly not CSF. These included standard solution phantoms, eyes, areas around the sinus and some noisy regions. The partial volume was accounted for by giving a weight of 1.0 to any voxel having an intensity greater than 0.77 and linearly weighting between 0.3 and 1.0 for voxels having an intensity between 0.32 and 0.77. As is obvious, the selection of these ranges was slightly arbitrary and it does effect the calculated CSF volume. The advantage is that by this method we are studying regions described by T2 intensities, which can be reproducibly selected, and which represent CSF volume.

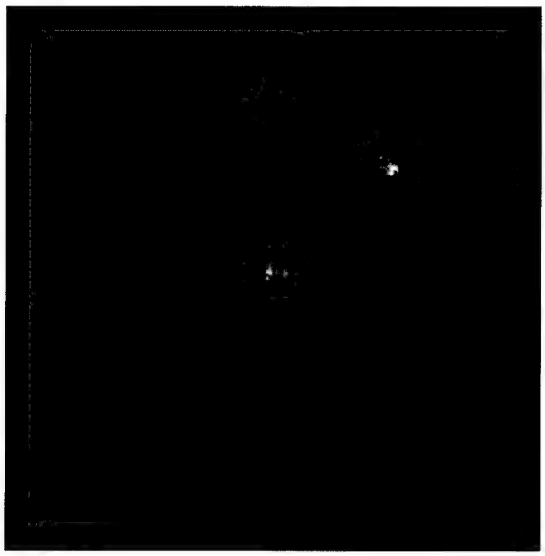
Figure A shows the image with an echo time of 30 ms and Figure B with an echo time of 120 ms. In figure B the CSF appears brighter and can be distinguished. Figure C is the normalized image and Figure D shows the CSF marked by our algorithm. The intensity in Figure D reflects the weighting criteria discussed above.



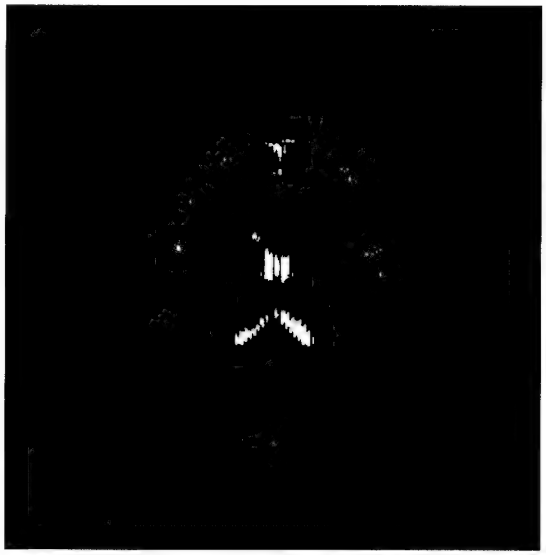
A. Te = 30 ms



B. Te = 120 ms



C. Normalized image



D. CSF image

Preliminary results on four subjects with the lowest AMS scores and two subjects with the highest scores are summarized in table 7. This data is not sufficient to draw any conclusions but they suggest that there may be no significant change in CSF volume after the high altitude exposure.

Table 7

Patient	CSF volume (cm3) Control day	CSF volume (cm3) After chamber study
Least sick 1	186	184
Least sick 2	228	230
Least sick 3	155	140
Least sick 4	282	263
Most sick 1 (1^{st} exp)	134	128
Most sick 1 (2^{nd} exp)	147	132
Most sick 2 (1^{st} exp)	168	169
Most sick 2 (2^{nd} exp)	169	176

Other results

Data pertaining to diet during the control and altitude day are also compiled from analyses of diet records. Specifically, amounts of carbohydrates, fats, protein, calories, sodium and potassium are obtained. The fluid intakes are available to be tabulated to compute fluid balance, once the collection of data is completed.

From the "correlative" tests we have other values to characterize the subjects. These include the hypoxic and CO_2 ventilatory response tests given on the control day, as well as the heart rate, blood pressure, perceived pain and catecholamine response to the cold pressor test. These are being compiled and data analysis will proceed when all data is collected.

The cognitive tests include the following seven tests as part of the Walter Reed Performance Assessment Battery (PAB) of tests utilized by the Army: a) Choice Reaction Time, b) Logical Reasoning, c) Delayed Recall, d) Code Substitution, e) Stroop, f) Stanford Sleepiness Scale and g) Profile of Mood States. The "AMS-C" and "AMS-R" scores, as obtained from the Environmental Symptoms Questionnaire, will be used in addition to the Lake Louise AMS scores to determine AMS severity. These are all compiled on appropriate software while they are given on the control day and three times during altitude exposure after 1,6, and 12 hour.

Various indices related to fluid homeostasis, in addition to the directly measured hormones, will be calculated from measurements being compiled. These include: sodium and potassium excretion and clearance, glomerular filtration rate, free water clearance from plasma and urine osmolality measurements and total blood volume. Most of these measures of fluid balance and regulation are available serially during the altitude exposure from analyses of the venous blood and urine samples.

All data is being compiled and stores on an EXCEL template. We have completed the formatting of data storage and it is accumulating as experiments are completed.

C. Recommendations to Statement of Work

The objectives of the original statement of work remain unchanged, i.e., to determine whether symptoms of AMS are related to a) menstrual cycle phases, b) the use of oral contraceptives and c) gender. We are on the schedule originally given to complete the study. The data collection is completed for the 18 men and for 19 women in both menstrual phases and two in the follicular phase. Thirteen women taking oral contraceptives have been tested. Nine have been tested during both high and low progestin levels inherent in their pill regimen plus four at one level only. During the past year it was decided, after discussions with the Army monitor, that testing at two progestin levels would give additional information, especially if these were women who were also tested when not on oral contraceptives. Six more pairs and three individual experiments remain to be completed. When completed, comparisons will be available between 18 men and 33 total women and 19 paired comparisons between luteal and follicular phases. Paired comparisons between 8 women on and off contraceptives will be available, as well as comparisons between 21 different individuals off the pill with 11 others taking contraceptives.

CONCLUSIONS

In 18 men and 31 women studied to date, we have observed the range of AMS scores expected when volunteers of this age range are randomly selected. It can be definitively stated that there is no difference in the severity of AMS symptoms during the luteal and follicular phases of the menstrual cycle in women. The data collected to date does not suggest that taking oral contraceptives will serve to reduce the AMS symptoms. Also, no

significant difference in AMS susceptibility between men and women has been demonstrated. Results pertaining to altitude–induced changes in ventilation, blood gases, urine volume and body water compartments are still not yet clear. It appears that women in the luteal phase have a tendency to increase their ventilation more at altitude than when in the follicular phase. This may be supported from subsequent analysis of the 3-breath N_2 test done serially at altitude. Extracellular water changes tend to be directly related to AMS severity in men, but not women. Total body water changes are directly related to AMS in all subjects. A decreased urine volume at altitude is associated with AMS more clearly in women who are not on oral contraceptives than in women who are on contraceptives and men. There is no evidence that the transcapillary exchange rate of circulating albumin is altered at altitude and variations in it and plasma volume changes do not appear to be responsible for the development of AMS. The arterial blood gas measurements demonstrate that AMS in these acute exposures is not related to pulmonary gas exchange deterioration.

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An abstract by the current investigators, presented at a national meeting, summarizing some preliminary findings from this study is given in Appendix 2.

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APPENDICES

Appendix 1(4 pages) and appendix 2 (1 page) follow:

Appendix 1

WORKING GUIDELINE FOR EXPERIMENTAL TASKS AND PROCEDURES

DAY 1 (CONTROL)

"Morning Baseline"procedures

6:00 - 6:30 AM	1)Subject voids overnight urine and measures volume 2) Drinks water (and/or breakfast drink) to total 1,000 ml (or as adjusted for sleep time) when added to urine volume 3) Eats standard breakfast and drinks water or juice, etc., in addition, to total 0.5% of body weight. Can have one cup of coffee/tea, if usual, included in the above

Subject reports to the chamber laboratory at 1:00 PM and remains there for the rest of that day.

1:00 -3:00 PM	1) Record body weight and attach EKG electrodes 2) Insert venous cannula 3) Venous blood draw, (if female, progesterone only) 4) Practice Symptom scores (LL, VA's, ESQ) 5) Practice Cognitive tests twice 6) HVR (poik, poik, iso) and HCVR and 3-breath N_2 and O_2 tests 7) Cold pressor test: measure baseline BP, HR, epi and norepi. Then BP and HR and pain index every min for 5 min and draw sample for epi and norepi during the last min.
3:30-4:00	(1) Void Urine and drink to equal volume (2) Eat snack (3) Record weight (4) Draw baseline for Evans, NaBr and D_2O
4:00	(5) Drink D_2O-NaBr cocktail, record exact time (6) Inject Evans, record exact time (e.g. 4:00 PM)
4:10	Venous blood (Evans) , record exact time
4:20	Venous blood (Evans) , record exact time
4:30	Venous blood (Evans) , record exact time
5:00	Venous blood (Evans) , record exact time
5:00 - 6:00	Check stick-on electrodes. Then subject rests quietly, lights out, to be at basal state for subsequent hormone draw, calibrate and update Consentius metabolic device
6:00-7:00 PM	**"Hour 12:00" Control measurements** 1)Venous blood (Evans, NaBr, D_2O, 6 hormones, extra plasma, elect, creat, PP, osmol, PD, Hct), record exact time 2) Spirometry 3) Symptoms (LL, VA's, ESQ)

4) Cognitive testing
5) Check "record" button on Consentius to record following resp. file
6) Anesthetic for arterial, calibrate and set end-tidals
7) Respiratory measurements (plus end-tidal, BP, HR)
8) Arterial Blood
9) "End test" on Cons. and save Cons. file to appropriate HRV directory and rename as "3-breath" for next test
10) 3-breath N_2 test (twice) and 3-breath O_2 (once), record end-tidal cals

(7:00) 11) Venous blood (Evans, NaBr, D_2O) , record exact time
12) Void urine, collect sample, (protein, elect, creat, osmol), and drink ad lib
13) Record weight
14) Record body temp

Remove catheter

(7:15-7:30) **Go to VAMC for baseline MRI**
Symptom scores (LL, VA's) after MRI
Prescribed evening meal after MRI

DAY 2 (ALTITUDE CHAMBER)

5:00 - 5:30 AM Subject arrives at chamber with overnight urine (if necessary)
1) Voids overnight urine (volume only)
2) Drinks water(and/or breakfast juice) if needed to total 1,000 ml with urine volume
3) Eats standard breakfast and drinks water or juice, in addition, to total 0.5% of body weight

5:30-6:30 4) Insert venous catheter
5) Venous blood draw, if female (progesterone only)

"Normoxia Baseline" measurements

6:30-6:45 1) Symptoms (LL+ VA's)
2) Void and drink

6:45-7:00 Enter chamber, ascent to 426 mm Hg (16,000 ft)
1) Set "Time zero" on clock
2) Record weight
3) Record body temp

7:30-8:00 Rest and lights out for subsequent hormones

"1 hr" measurements at altitude

8:00-9:00 AM 1) Venous blood (6 hormones, extra plasma, elect, creat, PP, osmol, PD, Hct)
2) Spirometry
3) Symptoms (LL, VA's, ESQ)
4) Cognitive testing
5) Check "record" button on Consentius to record following resp. file
6) Anesthetic for arterial, calibrate and set end-tidals
7) Respiratory measurements (plus end-tidal, BP, HR)

8) Arterial Blood
9) "End test" on Cons. and save Cons. file to appropriate HRV directory and rename as "3-breath" for next test
10) 3-breath N_2 test (twice) and 3-breath O_2 (once), record end-tidal cals
11) Record body temp

10:00 — 1) Void urine (0-3 hr interval) and collect (protein, elect, creat ,osmol) and drink
2) Record body weight

11:00 AM -12:00 — Lunch Time
12:30-1:00 — Rest and lights out for subsequent blood draw

"Hour 6" measurements at altitude

1:00-2:00 PM — 1) Venous blood (6 hormones, extra plasma, elect, creat, PP, osmol, PD, Hct)
2) Void urine (3-6 hr interval) and collect (protein, elect, creat ,osmol) and drink
3) Record body weight
4) Spirometry
5) Symptoms (LL, VA's, ESQ)
6) Cognitive testing
7) Check "record" button on Consentius to record following resp. file
8) Respiratory measurements (plus end-tidal, BP, HR)
9) "End test" on Cons. and save Cons. file to appropriate HRV directory and rename as "3-breath" for next test
10) 3-breath N_2 test (twice) and 3-breath O_2 (once), record end-tidal cals
11) Record body temp

3:30-4:00 — 1) Void urine (6-9 hr interval)and collect (protein, elect, creat, osmol) and drink,
2) Snack time
3) Record body weight
4) Draw baseline blood for D2O, NaBr, Evans
5) Drink D_2O-NaBr cocktail, record exact time

4:00 — 6) Inject Evans, record exact time (e.g. 4:00 PM)
4:10 — Venous blood (Evans) , record exact time
4:20 — Venous blood (Evans) , record exact time
4:30 — Venous blood (Evans) , record exact time
5:00 — Venous blood (Evans) , record exact time
5:00 - 5:30 — Check stick-on electrodes
5:30-6:00 — Subject rests quietly, lights out, to be at basal state for subsequent blood draw, calibrate and update Consentius

6:00-7:00 — **"Hour 12:00" Altitude measurements**
1) Venous blood (Evans, NaBr, D_2O, 6 hormones, extra plasma, elect, creat, PP, osmol, PD, Hct) , record exact time
2) Spirometry
3) Symptoms (LL, VA's, ESQ)

4) Cognitive testing
5) Check "record" button on Consentius to record following resp. file
6) Anesthetic for arterial, calibrate and set end-tidals
7) Respiratory measurements (plus end-tidal, BP, HR)
8) Arterial Blood
9) "End test" on Cons. and save Consc. file to appropriate HRV directory and rename as "3-breath" for next test
10) 3-breath N_2 test (twice) and 3-breath O_2 (once), record end-tidal cals

(7:00) 11) Venous blood (Evans, NaBr, D_2O) , record exact time
12) Void urine (9-12 interval), collect, (protein, elect, creat, osmol) and drink ad lib
13) Record body temp
14) Record weight

Remove catheter

7:00-7:15 Descend to "Albuquerque"

7:15-7:30 **Place subject on 13.5% O_2 and transport to VA Medical Center for MRI**
1) Symptoms (LL+VA) after MRI
2) Void urine and collect (volume, protein, creat, elect, osmol), record time after MRI

Appendix 2

Presented at Experimental Biology 98 meeting, San Francisco, CA, April, 1998.

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INCREASED PLASMA VOLUME (PV) AT SIMULATED ALTITUDE AND THE ONSET OF ACUTE MOUNTAIN SICKNESS (AMS).

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AMS is a syndrome that occurs in people who ascend to high altitude without taking time for proper acclimatization and includes headache, nausea and dizziness. Fluid retention is associated with AMS. However, whether the observed fluid retention is causal or secondary to AMS has not been established. Furthermore, the time course of the retention of fluid and development of symptoms has not been followed in the first 12 hrs of altitude exposure. We hypothesized that fluid retention, in this case demonstrated by an increased PV, would occur in persons who subsequently developed AMS. To test this hypothesis we studied 13 young healthy volunteers (6 men) before and during a 12 hr exposure to simulated high altitude (barometric pressure = 430 mm Hg). We measured PV by Evan's Blue at baseline, and in the last 3 hrs of the 12 hr altitude exposure. Also, at 1 hr altitude exposure, PV change from baseline was estimated by the hematocrit/hemoglobin ratio technique. After 9-12 hrs altitude exposure the change in PV from baseline was positively correlated with AMS symptom score ($r=0.87$, $p<0.001$). All subjects with a rise in PV from baseline developed marked symptoms of altitude illness. Furthermore, the relationship of the estimated PV change at 1 hr to the measured PV at 12 hr suggests that the mechanism responsible for retaining fluid is set in place early in altitude exposure, and before symptoms are apparent. Thus, it seems likely that fluid retention is not secondary to the development of symptoms in AMS.

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